Randomised trial of prophylactic daily aspirin in British male doctors

SIR,—There can be no doubt that the British trial (30 January, p 313) has made a great contribution to research into the effect of aspirin on the frequency of primary infarction and stroke. Both the extent and the duration of this study deserve peer recognition, and these results, acknowledged the world over, are of great scientific interest.

In contrast to the results obtained by the British research group, those produced by the American group clearly show a significant reduction in the rate of infarction in doctors who took aspirin, a result which ultimately led to the premature termination of the study.[1]

An attempt to explain these discrepancies reveals fundamental differences in the way in which these two major studies were carried out. The American study featured not only a considerably larger number of volunteers but also a true control group which took placebos according to a double blind study design. The British control group was merely recommended to avoid taking aspirin. Furthermore, during the six year study about 12% of the British control group changed over to the group taking aspirin, while 30% of the aspirin group stopped taking it. Also, part of the aspirin group transferred to a different formulation during the study and reduced the dose from 500 to 300 mg, thus destroying the comparability of the two groups. Moreover, the results of the study were projected arbitrarily on to a reference value of 10 000 man years.

It is at this point, if not sooner, that we must question the binding nature of a scientific study protocol. What is the claim to validity of a scientific study which is carried out according to criteria that change so frequently? The authors themselves are apparently aware of the shortcomings of their study and in their discussion readily refer to their American colleagues, whose results they consider more significant.

They observe that an unbiased and qualified evaluation of the side effects can be carried out only on the basis of a placebo group. Why did the British research group pass up the opportunity of gaining such important results? It is regrettable that the necessary further scientific analysis of the range of activity of aspirin in the primary prevention of infarction should be endangered so easily by a study protocol which is equivocal to say the least. This is all the more tragic if we consider the pioneering character of this British study in the discussion surrounding the use of aspirin in the primary prophylaxis of myocardial infarction.

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1 Steering Committee of the Physicians' Health Study Research Group. Preliminary report: findings from the aspirin component of the ongoing physicians' health study. *N Engl J Med* 1988;**318**:262-4.

AUTHORS' REPLY,—There were, as Dr Weber points out, major differences between the British and the United States studies of the prophylactic value of aspirin; but we do not need to look to these to account for the different results.

The main difference in the results (the apparent effect on the incidence of non-fatal myocardial infarction) can be attributed to chance. The results of both studies are statistically compatible with the idea that doses of aspirin of the order prescribed reduce the risk of non-fatal myocardial infarction by a third, which is close to the 32% recorded in a review of 31 randomised trials of aspirin and other antiplatelet drugs in the treatment of patients with a history of transient ischaemic attack, occlusive stroke, unstable angina, or myocardial infarction (30 January, p 320). We conclude, therefore, that aspirin has about the same relative effect irrespective of whether it is used prophylactically or therapeutically. Whether it reduces the overall mortality from vascular disease in people not at high risk of a myocardial infarction is another matter. Neither of the prophylactic trials suggests that it does, and it may be that the benefit in healthy people, who will have a relatively low risk of thrombosis, is partly counteracted by an increased risk of cerebral haemorrhage. It is, however, only reasonable to suppose that a reduction in non-fatal myocardial infarction is accompanied by some reduction in fatal myocardial infarction, as occurred in the treatment trials.

We are sorry that Dr Weber regards our study protocol as equivocal. The protocol may be open to criticism, but not, we think, because we failed to make it double blind. The nature and extent of the non-fatal side effects of aspirin have been shown by the double blind trials of aspirin in the treatment of myocardial infarction, and we saw no need to seek information about them. Our study was designed to see if aspirin given prophylactically would reduce the risk of death from vascular disease in people who had never previously had a myocardial infarct. We believed we could record death from vascular disease objectively and for this purpose it was not necessary to try to hold several thousand doctors to the daily use of a placebo. If we were to repeat the study we would again do it openly. What we would not do, however, would be to give aspirin to thousands of men without first finding out whether it caused them dyspepsia. The experience of the first six months of our trial showed that so many men reacted unfavourably within a matter of months that Hennekens (who had been working with us when the trial started and is a joint author of both papers) sensibly gave all the American volunteers a trial of aspirin before allocating them to aspirin or placebo. As a result a high proportion of non-compliers were weeded out before the study began.

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Audit of a surgical firm by microcomputer

SIR,—My friend Mr D C Dunn (5 March, p 687) has clearly made surgical audit his pastime. The vast number of figures produced reminds one of Lowry's paintings. What are the resultant alterations in his surgical practice? "The high incidence of chest and wound infections led us to put increased emphasis on measures that might reduce these problems. . . . Increased care was taken with wound haemostasis and remembering prophylactic antibiotics . . . complications were more likely to occur when many major operations were performed in a short space of time."

His enormous data input hardly justifies a need for such conclusions. Long before microcomputers wound infection rates were adequately reduced. Maybe his were unduly high in 1982?

But my main purpose in writing is to warn against the unlimited collection of figures. Limited resources are better directed into clinical work. The cult of numeracy in surgery has its serious limits. No two surgical units are alike. It is therefore not possible to argue from the figures of one to those of the other. Such a course is beset with pitfalls, not least illustrated by the occasion some years ago when two professors of surgery argued about the validity of each other's statistical methods.

New knowledge does not consist in the production of figures. If surgical audit is meant to show outsiders that surgeons keep their houses in order how will they prove that their indications for operations were right? In Mr Dunn's paper I cannot see the wood for trees. The danger lies in our official bodies requiring similar analyses from elsewhere only to have shown to them after a lot of labour and time that the collection of figures over a broad canvas has little practical value.

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AUTHOR'S REPLY,—I take it as a compliment to have my paper compared with the achievement of one of Lowry's paintings. Those who know me will be aware that my pastimes are quite different from that of "playing with audit." Nevertheless, I like to know what is going on in my unit. This has nothing to do with "official bodies." It is simply a question of taking a professional pride in what one is doing and making sure it is as good as possible. It is important that the machine is a microcomputer and is under our control. We forward what we choose to "outside bodies."

In retrospect our complication rates may have been slightly high in 1982. We found this out and we did something about it. Does Mr Weale know what his complication rates are? Can he be sure that there is nothing to be done to improve his practice? Possibly he is not interested in such questions, but I do not think he has any solid grounds for criticising others who are so interested.

When he states that "the enormous data input" is hardly justified by the results he has missed the point. No extra effort is now required to collect the data. We collect data to produce discharge summaries and have almost halved the time necessary for this exercise. The data are then easily available for any other purpose. We use them for monthly audit meetings, which I and my colleagues find useful and interesting. The computer reduces the time required to prepare for these meetings from several weeks to a few days. Can improving efficiency in our unit really be called a misuse of resources? Would the effort have been better spent producing more undetected complications? Mr Weale seems obsessed with "outsiders" and "official bodies," but we feel that our audit is something personal and private, which is of value to ourselves and makes life more interesting.

Mr Weale's worry about the unlimited collection of figures is nevertheless entirely in accordance with my own point of view. That is why I have taken the trouble to keep the data collected to a minimum and to develop a computer system which makes sure that less time is spent running the firm with it than without it. Mr Weale's fears about such efforts being wasteful were shared by us initially, but, after six years' experience, we have found the regular audit to be rewarding. None of our junior staff, secretaries, or consultants wish to return to the bad old days, with piles of notes lying around waiting for summaries to be written and no information available about the work we were doing.

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Reactions to contrast media

SIR,—Dr J F Reidy discusses the desirability of using the new low osmolar contrast media, which

are less likely to produce reactions in certain high risk patients such as those with asthma, cardiac or renal failure, or a history of such reactions (19 March, p 809). He states, quite rightly, that these media are still considerably dearer than the older agents but does not mention the quantity necessary to produce adequate radiographs.

Using only half the currently recommended dose (25 ml instead of 50 ml), we have shown that in most patients this amount produces diagnostically acceptable urograms.[1] Our conclusion was that if this regimen is followed it should prove possible to use the safer media for all patients and that although this would cost more than at present it should prevent the rare serious complications including the occasional death.

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1 Eyes BE, Goldman M, Nixon TE, Scally J, Brown A. Low dose low osmolar intravenous urography. *Clin Radiol* 1987;**38**: 403-5.

Early growth in diabetic pregnancy

SIR,—Dr Minna Bloch Petersen and colleagues (27 February, p 598) seek to show that delayed fetal growth in early pregnancy, which they report as being more common in the offspring of diabetic women, is a cause of developmental delay at age 4.

In drawing this conclusion, however, they ignore a crucial part of their own data—namely, that only 5% of the diabetic mothers were educated to college standard compared with 18·6% of the non-diabetic women. Since the only significant difference between the Denver test scores of the two groups of children was in language and speech development, it seems at least as likely that this was related to levels of sophistication in language use in the mothers as it was to intrauterine growth delay. It is, of course, true that there was apparently a difference within the diabetic group between those children in whom growth was delayed and those in whom it was not; the numbers of children in these two groups who failed the Denver test, however, were small (eight and two respectively), so that the probability of a type 2 error must be high if some other factor, such as maternal educational level, is operating.

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AUTHOR'S REPLY,—Dr R A Fisken is right in his remarks on the educational difference between diabetic and non-diabetic mothers (2·4% and 18·6% educated at college level respectively).

In our study we found that as a group the children of diabetic mothers scored only slightly (and not significantly) worse than those of non-diabetic mothers. Secondly, the results of the Denver developmental screening test were not associated with the level of education of the mothers. Thirdly, the children of diabetic mothers with normal early fetal growth had scores very similar to those of the children of non-diabetic mothers, and no significant difference was found in language and speech development (the difference in the educational level of the mothers in the two groups being the same as mentioned above). Finally, the poor performance in the Denver developmental screening test in the diabetic group was apparently confined to those children who had been small in early fetal life. Only 67·7% of these children had normal test scores and 23·5% failed in language and speech, compared with 92% and 4% respectively of the children with normal early fetal growth. The educational level of the two groups of diabetic mothers did not differ significantly.

We are well aware of the small number of children failing in language and speech and are aware that factors other than the mother's level of education may be operating—for example, different types of kindergartens. The overall test result of the two diabetic groups based on 34 and 50 children indicates, however, that early fetal growth delay may influence later development.

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HIV infection: risks of false positive serology

SIR,—Professor A A Glynn and Dr P P Mortimer (5 March, p 714) are right to emphasise that most commercially available HIV antibody tests are both highly sensitive and highly specific. If two different systems are used the risk of a false positive is about 1 in 40 000 and if three different systems are used about 1 in 1 million.

Nevertheless, most virologists concerned in rubella antibody screening have encountered patients who have been reported as having rubella antibodies but have subsequently acquired rubella in pregnancy. In most cases this error has not been due to any failure of test systems or to loss of rubella antibodies but has been the result of other factors.[1,2] These include, for example, incorrect labelling of blood containers in outpatient departments, technical errors, perhaps due to the interruption of a busy medical laboratory scientific officer performing the test, or even the issuing of an incorrect report due to a clerical error.

In view of the serious medicolegal consequences as well as the distress which may result from a false positive HIV test, we recommend that the risks should be minimised by issuing only a preliminary report when a serum sample is found to be positive by three tests. A final report can then be issued when the results have been confirmed by testing an additional serum sample from the same patient.

Since we routinely perform tests three times a week (or immediately in an emergency) and as clinicians can readily make arrangements to have their patients retested within a few days, our system need not result in there being undue delay before a final report is issued.

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The use of varicella vaccine in Britain

SIR,—Drs Carol Joseph and Norman Noah provide valuable information on the clinical impact of varicella in Britain (5 March, p 673). They rightly point out that varicella accounts for a higher mortality than mumps, which we are about to attempt to prevent with the combined measles-mumps-rubella vaccine, but seem reticent to discuss their data in the context of prevention by vaccination.

We agree that a mass vaccination programme using the live varicella vaccine cannot be advocated until the questions of safety and long term efficacy have been resolved. A cost-benefit analysis[1] has shown a benefit ratio of 7:1 for mass vaccination in the USA, but this benefit was mainly derived from costs to the family arising from the home care of sick children, not savings on medical costs. Since social conditions in Britain are different the financial argument will be strong only if the cost of the vaccine is comparable with that of other vaccines.

The most interesting dilemmas for licensing authorities relate to the long term effects of the vaccine on the epidemic pattern of varicella and on herpes zoster. Recent reports have shown that the vaccine virus can become latent and cause zoster,[2] even in healthy vaccinees,[3] although probably less frequently than wild type virus. More intriguingly, vaccination may not always protect from superinfection with wild type varicella zoster virus, which later can cause zoster.[2] Paradoxically, only the experience gained through more general use of the vaccine will provide the necessary information about its long term effects on varicella and zoster.

The case for vaccination of immunocompromised patients is totally different. This is a steadily increasing group of patients who carry a high risk of life threatening complications associated with varicella.[4] Undoubtedly, it is preferable to prevent these complications by vaccination rather than to rely on postexposure prophylaxis and treatment with zoster immune globulin or acyclovir. In fact, the vaccine is also effective for postexposure prophylaxis up to four days after contact.[5]

The vaccine has now been used in immunocompromised patients for over 10 years and has proved to be both safe and effective.[6] Our own experience with this vaccine[7] in paediatric oncology patients is that individual responses vary greatly but even in those with poor responses the vaccine appears to confer considerable protection. Good antibody concentrations have been maintained for over six years in some of our vaccinees after a single vaccine dose, although about 40% have shown poor or rapidly waning responses. Regular monitoring of immunity, combined with a booster vaccination, is therefore necessary.

It may not be a perfect vaccine but it is the best we have, and, while mass vaccination cannot be advocated on present evidence, there is no doubt that selected high risk groups would greatly benefit from this vaccine, particularly children with malignancies. The problem for British paediatricians who manage immunocompromised children is that the vaccine is not freely available here. The relevant authorities should give serious thought to licensing the varicella vaccine for selective use, as is done in several European countries and shortly will be in the United States.

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